

REMARKS

Claims 1 to 20 are currently pending in the application. All of the claims were rejected. Claims 1, 12, 13, 14, 16, 17 and 19 have been amended. All of the amendments find full support in the specification and drawings as filed. No new matter has been entered. In view of the above amendments and following remarks, Applicants respectfully submit that this application is in condition for allowance. Accordingly, reconsideration and a timely notice of allowance are respectfully requested.

Claim Amendments

Claim 1 has been amended to recite “wherein the at least one integrator is controlled only by a separate one of the plurality of triggers in response to scattered light incident on one of the scatter detectors.” Claim 12 has been amended to recite “wherein the at least one integrator is controlled only by the trigger in response to scattered light incident on one of the scatter detectors.” Claim 19 has been amended to recite “wherein each of the plurality of integrators is controlled only by a separate one of the plurality of triggers in response to scattered light incident on one of the scatter detectors.” Full support for these amendments is found in the specification and drawings as filed, for example on page 8, lines 10 to 21 and page 13, lines 14 to 28.

Claim 13 has been amended to recite “wherein a spacing and an order of the plurality of excitation light beams on the fluorescently labeled particle do not have to be predetermined prior to usage of the system.” Claim 16 has been amended to recite “dynamically assigning fluorescence detected in steps c) and f) to specific ones of the plurality of dyes depending on the excitation light sources.” Claim 19 has also been amended to recite “wherein the output of each integrator is dynamically assigned to one of the fluorescent labels depending on which laser is interrogating the particle.” Full support for these amendments is found in the specification and drawings as filed, for example on page 14, lines 15 to 17, page 17, lines 1 to 7 and 20 to 24, page 19, lines 13 to 28, and page 23, lines 27 to 30.

Claim 14 has been amended to recite “a plurality of lasers, at least one laser exciting a plurality of dyes.” Additionally claim 14 has been amended to recite “the multi-bandpass filter passing a number of discrete wavelength bands to the photomultiplier tube, the number being equal to the number of dyes detectable by the detector.” Finally, claim 14 has been amended to recite “wherein the number of fluorescence detectors is equal to the number of dyes excited by the laser that excites the most dyes.” Full support for these amendments is found in the specification and drawings as filed, for example, on page 14, lines 23 to 26 and on page 19, lines 4 to 12 of the specification.

Claim 17 has been amended to recite “wherein at least two dyes are excited by the first excitation light source or the second excitation light source.” Full support for this amendment is found in the specification and drawings as filed, for example, on page 16, lines 11 to 17.

Additionally, claims 1 and 13 have been amended to recite “a plurality of triggers, each of the plurality of triggers being coupled to a separate one of the plurality of scatter detectors.” Full support for these amendment is found in the specification and drawings as filed, for example, on page 15, lines 19 to 26. Finally, claim 12 has been amended for clarity to change photodiodes to “scatter sensors” which are further referenced in claim 12.

No new matter has been added. Applicants respectfully request entry of the above claim amendments.

Rejection Under 35 U.S.C. §112

The Examiner rejected claim 14 under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner states that the limitation “exciting a maximum number of dyes” is unclear, because it is unclear whether the Applicants are referring to the total number of excitable dyes located within the particle under test, or the total number of dyes excitable by each laser. In view of the amendment to claim 14, Applicants respectfully traverse this rejection.

Claim 14 has been amended to clarify that the number of fluorescence detectors is equal to the number of dyes excited by the laser that excites the most dyes. Claim 14 has also been amended to clarify that at least one laser excites a plurality of dyes. Additionally, claim 14 has been amended to clarify that the number of bands passed by the multi-bandpass filter is equal to the number of dyes detectable by the detector. As explained above, all of the amendments find full support in the specification and drawings as filed. No new matter has been added.

In view of the amendments to claim 14, Applicants respectfully submit that claim 14 particularly points out and distinctly claims the subject matter which Applicants regard as the invention. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Claim Rejections Under 35 U.S.C. §101

The Examiner rejected claims 16 and 17 pursuant to 35 U.S.C. §101 as being directed to non-statutory subject matter. The Examiner states that identifying, determining, devising, evaluating, detecting, assigning, etc. are not sufficient to constitute a tangible result since the outcomes of the method steps has not been used in a disclosed practical application nor made available in such a manner that its usefulness in a disclosed practical application is realized. Applicants respectfully traverse this rejection.

Both claims 16 and 17 are directed to methods for measuring the fluorescence of a particle having a plurality of dyes. As seen from pages 1 to 3 of the specification as filed, the use of fluorescently coded particles, such as in flow cytometry, is well known. Applicant's method for measuring fluorescence will find widespread application to those skilled in the art.

The expansive language of 35 U.S.C. §101 includes "anything under the sun that is made by man." *Diamond v. Chakrabarty*, 447 U.S. 303, 308-09, 206 USPQ 193, 197 (1980). In *Chakrabarty*, 447 U.S. at 308-309, 206 USPQ at 197, the court stated that abstract ideas, laws of nature and natural phenomena are not patentable. Applicants respectfully submit that the methods of claim 16 are not abstract ideas, laws of nature or natural phenomena, but rather clearly defined methods for obtaining a specific, useful result. Accordingly, Applicants respectfully submit that claims 16 and 17 meet the requirements of 35 U.S.C. §101.

Therefore, Applicants respectfully request that this rejection be withdrawn.

Claim Rejections Under 35 USC §103

The Examiner rejected claims 1 to 3, 7 to 16 and 19 under 35 U.S.C. §103(a) as being unpatentable over Martin et al. (U.S. Patent No. 4,573,796) in view of Hansen et al. (U.S. Patent No. 4,284,412). In view of the amendments to claims 1, 12, 13, 14, 16, and 19, Applicants respectfully traverse this rejection.

The present invention is directed to a system for measuring the irradiance of a fluorescently labeled particle, comprising: a cytometric flow chamber; a plurality of excitation light sources; a plurality of scatter detectors, each configured to detect light from only one of the plurality of excitation light sources; a plurality of triggers, each trigger being connected to a separate scatter detector; a collection optics to collect emissions from the fluorescently labeled particle; at least one fluorescence detector, the at least one fluorescence detector being configured to respond only to a discrete number of wavelength bands; and at least one integrator connected to the trigger and the at least one fluorescence detector, for recording the output of the at least one fluorescence detector in response to a signal from the trigger. Because there is a scatter detector corresponding to each excitation light source, and because the fluorescence detectors are configured to respond only to a discrete number of wavelength bands, precise alignment and spacing of the excitation light sources is not necessary. Accordingly, the system can accommodate excitation light source or core velocity drift.

Compared to the prior art, the system of the present invention has an increased range over which the lasers can be aligned to obtain good fluorescence information. It is not necessary to precisely align all of the excitation light sources to focus on the same point in the flow chamber or to have a precise spacing along the flow path. Additionally, because there is a scatter detector corresponding to each excitation light source, the order of the excitation light beams need not be known prior to use of the system, as the detected fluorescence can be dynamically assigned based upon the excitation light source that triggered integration of detected fluorescence.

Martin is directed to an apparatus for eliminating background interference during fluorescence measurements in a multiple laser flow cytometer by modulating one or more excitation light sources depending on the position of a particle. In contrast to the presently claimed invention, the apparatus of Martin requires preexisting knowledge of the separation between excitation light sources, and therefore cannot accommodate excitation light source or core velocity drift during the course of an experiment. As explained in col. 4, lines 60 to 63, “the first gate signal is, effectively, delayed for a time sufficient for first biological particle 20 to travel the distance S from the first light beam 18 to the second light beam 50.” As seen in col. 4, line 35 to col. 5, line 10, a delay system relying on the known distance between excitation light sources, coupled to first and second modulators and gate signal generators to control the integrators is key to achieving the object of the invention. Moreover, the integrators are controlled by multiple triggers in response to light incident on multiple scatter detectors, thereby requiring precise alignment.

Accordingly, Applicants respectfully submit that Martin et al. fail to teach or suggest a system “wherein the at least one integrator is controlled only by a separate one of the plurality of triggers in response to scattered light incident on one of the scatter detectors” as recited in claim 1; a system “wherein the at least one integrator is controlled only by the trigger in response to scattered light incident on one of the scatter detectors” as recited in claim 12; or a system “wherein each of the plurality of integrators is controlled only by a separate one of the plurality of triggers in response to scattered light incident on one of the scatter detectors” as recited in claim 19; or a system “wherein a spacing and an order of the plurality of excitation light sources do not have to be predetermined prior to usage of the system” as recited in claim 13.

Additionally, Applicants respectfully submit that Martin et al. fail to teach or suggest the step of “dynamically assigning fluorescence detected in steps c) and f) to specific ones of the plurality of dyes depending on the excitation light sources” as recited in claim 16 or a system “wherein the output of each integrator is dynamically assigned to one of the fluorescent labels depending on which laser is interrogating the particle” as recited in claim 19.

Hansen et al. teach a flow cytofluorometric apparatus for processing blood. As seen in

Fig. 1 and col. 4, lines 32 to 44, two lasers are precisely oriented to focus on the same point in the flow chamber. As seen in col. 4, lines 49 to 54, scatter from both lasers incident on three different scatter detectors are used to control integration. Applicants respectfully submit that Hansen et al. fail to remedy the defects of Martin et al. Therefore, Applicants respectfully submit that claims 1, 12, 13, 16 and 19 are patentable over Martin et al. and Hansen et al., either alone or in combination.

Additionally, Applicants have amended claim 14 to recite that at least one laser excites a plurality of dyes. Applicants respectfully submit that neither Martin et al. nor Hansen et al. teach or suggest the use of a single laser to excite more than one dye. Moreover, Applicants respectfully submit that neither Martin et al. nor Hansen et al. teach or suggest “wherein the number of fluorescence detectors is equal to the number of dyes excited by the laser that excites the most dyes” as recited in claim 14.

Claims 2, 3, 7 to 11, and 15 depend from claims 1 and 14 and by definition contain all of the limitations of claims 1 and 14. Therefore, Applicants respectfully submit that claims 2, 3, 7 to 11, and 15 are patentable over Martin et al. and Hansen et al. for the reasons given above regarding claims 1 and 14 as well as because of the additional limitations contained therein.

Accordingly, Applicants respectfully request that the rejection of claims 1 to 3, 7 to 16 and 19 under 35 U.S.C. §103(a) be withdrawn.

The Examiner rejected claims 4 and 6 under 35 U.S.C. §103(a) as being unpatentable over Martin et al. (U.S. Patent No. 4,573,796) in view of Hansen et al. (U.S. Patent No. 4,284,412) and further in view of Pinkel (U.S. Patent No. 4,988,619). Applicants respectfully traverse this rejection.

Claims 4 and 6 depend from claim 1 and by definition contain all of the limitations of claim 1. As explained above with regard to claim 1, Martin et al. and Hansen et al., taken alone or in combination, fail to teach a system “wherein the at least one integrator is controlled only by a separate one of the plurality of triggers in response to scattered light incident on one of the scatter detectors.”

Pinkel is directed to a flow cytometry apparatus with an obstruction across the flow chamber to create a one dimensional convergence of a sheath fluid to orient flat cells. As seen in Fig. 1, and col. 2, lines 31 to 44, Pinkel only teaches the use of a single laser. Applicants respectfully submit that one skilled in the art would have no motivation to combine Pinkel with the multi-laser systems of either Martin et al. or Hansen et al. to remedy the defects of Martine et al. and Hansen et al.

Therefore, Applicants respectfully request that the rejection of claims 4 and 6 under 35 U.S.C. §103(a) be withdrawn.

The Examiner rejected claim 5 under 35 U.S.C. §103(a) as being unpatentable over Martin et al. (U.S. Patent No. 4,573,796) in view of Hansen et al. (U.S. Patent No. 4,284,412) in further view of Kramer (U.S. Patent No. 6,743,634). Applicants respectfully traverse this rejection.

Claim 5 depends from claim 1 and by definition contain all of the limitations of claim 1. As explained above with regard to claim 1, Martin et al. and Hansen et al., taken alone or in combination, fail to teach a system “wherein the at least one integrator is controlled only by a separate one of the plurality of triggers in response to scattered light incident on one of the scatter detectors.”

Kramer is directed to a method and apparatus for differentiating blood cells using back-scatter. As shown in Fig. 1, and discussed in col. 7, lines 19 to 28 two different lasers are used, but are oriented to be collinear. Applicants respectfully submit that Kramer fails to remedy the defects of Martin et al. and Hansen et al.

Accordingly, Applicants respectfully request that the rejection of claim 5 under 35 U.S.C. §103(a) be withdrawn.

The Examiner rejected claims 17 to 18 and 20 under 35 U.S.C. §103(a) as being unpatentable over Martin et al. (U.S. Patent No. 4,573,796) in view of Hansen et al. (U.S. Patent No. 4,284,412) and further in view of Hoffman (U.S. Patent No. 5,682,038). Applicants

respectfully traverse this rejection.

Claim 17, as amended, recites “the number of fluorescence detectors being equal to the larger of the maximum number of dyes stimulated by the first excitation light source and the maximum number of dyes stimulated by the second excitation light source” and “wherein at least two dyes are excited by the first excitation light source or the second excitation light source.” Thus, there are less detectors than total dyes detectible. As explained on page 23, line 30 to page 24, line 2 of the specification, “the use of multi-bandpass filters in conjunction with fewer photomultiplier tubes and associated electronics results in significant cost and space savings.

Applicants respectfully submit that Martin et al., Hansen et al. and Hoffman fail to teach or suggest a system that uses a number of photodetectors that is less than the total number of dyes being detected. Accordingly, Applicants respectfully submit that claim 17 is patentable over Martin et al., Hansen et al. and Hoffman, both alone and in combination.

Claim 18 depends from claim 17 and by definition contains all of the limitations of claim 17. Accordingly, Applicants respectfully submit that claim 18 is patentable over Martin et al., Hansen et al. and Hoffman for the reasons given above for claim 17 as well as because of the additional limitations contained therein. In particular, claim 18 recites “wherein at least one of the plurality of fluorescence detectors comprises a filter that only passes light emitted by a first dye upon excitation by the first excitation light source and light emitted by a second dye upon excitation by the second excitation light source.” Applicants respectfully submit that Martin et al., Hansen et al. and Hoffman fail to teach or suggest the use of a multi-band pass filter and therefore fail to teach or suggest this limitation.

Claim 20 depends from claim 19. As explained above, claim 19 is patentable over Martin et al. and Hansen et al., because neither of those references teach or suggest a system “wherein each of the plurality of integrators is controlled only by a separate one of the plurality of triggers in response to scattered light incident on one of the scatter detectors.”

Hoffman is directed to a flow cytometry system that is excited by two lasers. However, the system does not have separate scatter sensors configured to detect light from each of the lasers. Accordingly, Applicants respectfully submit that Hoffman fails to remedy the defects of

Martin et al. and Hansen et al. with regard to claims 19 and 20.

Accordingly, Applicants respectfully request that the rejection of claims 17 to 18 and 20 under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

The Applicants believe that all pending claims are in condition for allowance and such action is earnestly requested. If the present amendments and remarks do not place the Application in condition for allowance, the Examiner is encouraged to contact the undersigned directly if there are any issues that can be resolved by telephone with the Applicants representative.

A one month extension fee of \$120 is believed due with this Response and Amendment. The Commissioner is hereby authorized to charge payment of this fee and any other fees due with this communication to Deposit Account No. 19-2090.

Respectfully Submitted,

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Date: January 22, 2007

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